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14. ABSTRACT

This report represents the fifth in a multi-year effort to improve outcomes in patients with traumatic brain injury (TBI) utilizing human and animal models. The first two years focused on infrastructure development, development of a basic science protocol, development and institution of two human use protocols, staff acquisition, equipment purchase and development of a Brain Resuscitation Registry (BRR) to provide structure and linkage capabilities for data collection and outcome reporting. Year 3 accomplishments included the ongoing enrollment of subjects in the human use protocols focusing on the inflammatory process following TBI and vital sign response to trauma, development and implementation of 2 retrospective human use protocols, processing of specimens for the Cytokines sub-project, further development of the BRR and initiation of the basic science model including both small and large animal models of polytrauma. During Year 4 the existing human use protocols concluded data collection and neared finalization of data analysis, and a new protocol was proposed. Progress continued in BRR development and reporting, and the animal sub-project neared completion. Year 5 saw completion of data analysis for the Cytokines and Animal sub-projects, ongoing analysis of the Vital Signs sub-project, and continued development of the final human use sub-project. A no-cost extension was granted in September 2012, to allow for completion of the final human use protocol.

15. SUBJECT TERMS
Traumatic Brain Injury (TBI); vital signs; cytokines; pre-hospital care; polytrauma

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INTRODUCTION

Traumatic Brain Injury (TBI) is the primary cause of trauma mortality in both civilian and military populations, a major source of long-term disability world-wide and a substantial independent cause of death in the U.S. The dominance of TBI in trauma epidemiology is due to our inability to treat primary central nervous system injury and the realization that the phenomenon of secondary brain injury (pathology at the metabolic, cellular, vascular and tissue levels) begins within seconds after the primary trauma and plays a profound role in the subsequent evolution of TBI. This multi-year effort to improve outcomes in TBI patients focused creation of an infrastructure necessary to associate elements of care for the TBI patient with specific and relevant outcomes, including establishment of a centralized Brain Resuscitation Registry (BRR) for data capture, deployment of equipment to capture continuous pre-hospital and in-hospital vital signs, and development of human use and basic science models.

Targeted efforts over the life of the project have included: a human use protocol to examine the contribution of inflammatory cytokines after TBI, retrospective protocols to examine the contribution of oxygen delivery and surgical timeframes to outcome from TBI, and both small and large animal sub-projects of controlled cortical impact. During the fourth year of the project, the existing human use protocols completed data collection and focused on analysis, and an additional human use protocol was identified and submitted for approvals. The animal models neared completion of development and the BRR continued development with a focus on reporting structure. A no-cost extension for the 5th year of the project allowed for finalization of data analysis for sub-projects initiated in years 1 through 4 and further development and IRB approval of a final human use sub-project. A 20 month no-cost extension was approved in September of 2012, to allow for completion of the final human use protocol

BODY

This is the annual report for Year 5 of a multi-year project. Table 1 below reflects the adjusted Project Milestones Timeline based on the actual funding award date of September 17, 2007. Start and finish date columns reflect target timelines while subsequent columns reflect actual task completion dates. Research progress is further summarized by the itemized sub-projects following the table.

Table 1: Timeline

Activity Name	Target Completion	Actual Completion
Vital Signs Sub-project		
**Complete matching of 2009 cases	16-Oct-2010	1-Oct-2010
**Development of real-time ICU Team View	16-Oct-2010	1-Oct-2010
**Development of TBI prediction methods and algorithms	16-Oct-2010	On-going
**Complete matching of 2010 cases	31-Mar-2011	01-Apr-2011
***Initial IRB approvals*	31-Jan-2008	02-Apr-2008
Cytokines Sub-project		
**Purchase of final assay kits	15-Apr-2011	01-Dec-2010
**Completion of assay processing	15-Apr-2011	04-Jan-2011
**Completion of data analysis	15-Feb-2012	15-Mar-2012
***Initial IRB approvals*	31-Jan-2008	29-Jul-2008
Brain Resuscitation Registry		
**Implementation of reporting process	15-Jan-2011	12-Jan-2011
**On-going refinement of reporting process	15-Oct-2011	01-Jul-2012
Retrospective Subprojects: **TBI and Fracture Fixation** *and* **TBI, Oxygenation and Outcomes**		
**Submission of abstracts	15-Jan-2011	04-Jan-2011
**Manuscript submission	1-Nov-2011	01-Apr-2012
***Initial IRB approvals*	15-Jan-2010	29-Mar-2010
Animal Subprojects		
**Continue development of rat polytrauma model	16-Oct-2010	01-May-2011
**Initiate rat protocol	15-Apr-2011	01-May-2011
**Completion of data collection	15-Sept-2011	01-Feb-2012
**Initiate pig protocol	15-Jan-2011	01-April-2011
**Completion of data collection	15-Sept-2011	01-Oct-2011
**Obtain CCI device		10-Jan-2011
***IRB approvals*	01-Oct-2007	26-Feb-2008
TCD and BAM sub-project		
**Submission of protocol to IRB	16-Oct-2010	21-Feb-2011
**Submission of protocol to USAMRMC	30-Nov-2011	05-April-2011
**Initiate protocol	24-Sep-2012	
**Complete Subject Enrollment	24-Sept-2013	
**Complete Follow-up Interviews	24-Mar-2014	
**complete Analysis and final reporting	24-May-2014	
***UMB IRB approval*		25-Mar-2011
***USAMRMC HRPO approval*		19-Dec-2011

All human sub-projects have received IRB approval from the University of Maryland (UMB), IRB and the USAMRMC ORP, HRPO prior to implementation.

Sub-project 1: Vital Signs Data in Trauma Patients

This project was initially approved by UMB, IRB and USAMRMC ORP, HRPO upon continuing review on 2/21/08. This study was then re-assigned to the current project "Early Support of Intracranial Perfusion," on 2/26/08.

During Year 1 several amendments were made to the project including a waiver of informed consent. An amendment was also approved in October 2010 to increase subject enrollment to a total of 14,000 subjects. The most recent annual renewal for this protocol was submitted to UMB IRB in November and approved for continuation on 11/09/11. The continuing review report was submitted to USAMRMC ORP, HRPO on 11/23/11 and the acceptance memorandum received on 12/16/11.

Pre-hospital Vital Signs Data Collection (VSDC) system

During Year 1 emphasis was placed on the development of equipment and working with pre-hospital providers to expand capabilities to obtain pre-hospital vital signs (VS) data.

Year 2 focused on further development of pre-hospital VS analysis to allow auto cleaning of VS artifacts. Critical episodes of hypoxia (SpO2 <95%, <90% <75%, hypotension (SBP<90; <100 mmHg) and tachycardia (HR>120, >110,>100 bpm) were identified. Available pre-hospital cases were linked with trauma registry data for identification of outcomes such mortality, hospital /ICU length of stay, admit and discharge Glasgow Coma Scale (GCS) score, brain injury status (AIS-head), and ISS. In addition, review of medical records was completed to identify pre-hospital LSI (life saving interventions) and in-hospital emergency LSI during the first 4 hours.

During Year 3 a new LifePack system was introduced, and efforts focused on continued retrieval of these data and matching to potential subjects. Analysis was initiated based on vital sign waveform data collected in the pre-hospital management and in the first 60 minutes after admission to identify trends and prediction value of waveforms as compared to need for LSIs and outcomes.

During Year 4, approximately 250 pre-hospital VS case data were collected and matched with in-hospital Shock Trauma Center (STC) patient records. One hundred ninety –nine records were matched to STC patients and we were able to match 175 (88%) of these cases with in-patient and trauma registry outcomes data. The charts are currently being searched to obtain the pre-hospital run sheets and the timing and occurrence of LSIs. Once the data set has been validated then our existing outcome prediction software will be used to determine specificity and sensitivity (area under Receiver Operator Characteristic curve) of LSIs and outcome measurements.

Also during Year 4 a new proposal based on this work, *Continuous Non-Invasive Monitoring and the Development of Predictive Triage Indices for Outcome following Trauma* (U of MD PI Colin F Mackenzie) was funded by USAF (FA 8650-11-2-6D01).

During Year 5, previously collected TBI patient VS data sets were utilized to develop machine learning models for prediction of morbidity at 3 months (GOSE) and mortality. The results of this analysis were presented at the International Machine Learning Conference in Berlin Germany on July 15/16, 2012 and submitted for publication. Efforts have also focused on the development of imputation methods for estimating missing ICP values in VS data sets, providing a potentially a

critical stream of measurements for guiding clinical interventions and monitoring traumatic brain injuries.

In-hospital Vital Signs Data Collection (VSDC) system and Shock Trauma Physiological (STP) Registry

A limited system for VS data collection was in existence prior to the reassignment of this sub-project to the larger study. Therefore, emphasis in Year 1 was on system upgrades and expansion of VSDC capabilities. Expansion of the VSDC system from initial location in the Trauma Resuscitation Unit (12 admission bays and 6 operating bays) to a total of 54 critical care bays/beds also occurred during Year 1. Data mining was then initiated and preliminary algorithms were developed.

During Year 2 the VSDC system was further developed. Due to the low return on consent forms from prospective subjects, an amendment for a waiver of consent was submitted and approved by both UMB and USAMRMC.

In Year 3, based on the gap analysis, our research findings demonstrated the following:

1) The dose of patient VS above or below a critical limit (SBP<90, ICP>30, CPP<50 etc.) was determined to be a better predictor than the signal value alarm for patient outcomes (mortality, length of stay and 3, 6, 12 month GOSE).
2) It is difficult to quickly identify the patterns of multi-VS critical episodes at a glance for the duration of 12/24 hours.
3) For real-time ICU management it is important to show a quick overview of the patient in the unit. To address the above challenges we developed a real-time ICU Team View (ICUTV) which provides at-a-glance views of the 12 bed ICU VS trends and critical episodes. The ICUTV was deployed at the STC Neuro Trauma ICU with secured access made available to the remote physician office.

During Year 3, development of computer assisted auto patient physiological (VS) data identification software was also completed and introduced. This software facilitated the matching of 99.2% of the trauma admissions and the ultimate enrollment of 4,995 study subjects meeting study criteria. With improvements in the ability to accurately identify study subjects, a protocol modification is planned for the first quarter of Year 4 to increase the number of data sets available for analysis

By the end of Year 4, pre-hospital and admission VS data for more than 13,000 trauma patients admitted to the Shock Trauma Center (STC) in 2009 and 2010 were obtained from the trauma registry and analyzed using Receiver Operator Characteristic curves to predict the need for the LSI of a blood transfusion. Blood bank records identified those patients in this cohort who were alive on arrival, acutely hemorrhaging, and received blood and blood products within the first 24 hours. Findings indicated that pre-hospital and STC admission Shock Index (SI = heart rate/systolic blood pressure) had an 86% sensitivity and 81% specificity to predict blood and blood product use within 24 hours of STC admission (area under the Receiver Operator Characteristic curves of 0.72 and 0.78 respectively). The importance of this finding is that a 20-30 minute 'heads up' in advance of casualty arrival, obtained by automated SI decision- assist communicated from the field to the blood bank, would allow for a full range of blood products to be thawed or otherwise processed to supply coagulation factors such as plasma and platelets in near equivalence with red cells.

During Year 5, on-going analysis continued utilizing this data set in the development of prediction models as described. Additional funding is anticipated from USAF (FA8650-11-2-6D11) to examine Pre-Hospital Data collection, titled *Predicting Casualty Blood Product Needs Using Prehospital Vital Signs* (U of MD PI Colin F Mackenzie). In addition, vital signs analyses and decision support were used in further new funding obtained from the Office of Naval Research (ONR) (N00014-12-C-0120), *Autonomous Critical Care System.*

Sub-project 2: Early Support of Intracranial Perfusion – Cytokines

The protocol was initially submitted to UMB IRB on 3/20/08 and after requested revisions the final protocol was approved by UMB, IRB on 7/28/08 and USAMRMC ORP, HRPO on 7/29/08. The most recent annual renewal for this protocol was submitted to UMB IRB on 01/17/12 and approved for continuation on 01/19/12. The continuing review report was submitted to USAMRMC ORP, HRPO on 03/07/12 and the acceptance memorandum received on 06/04/12

Much of Year 1 focused on the standardization of policies and procedures for recruitment, specimen and data collection. The sub-project coordinator was assigned and identified research staff trained on recruitment and specimen/data collection procedures. Standardization of procedures for handling of collected specimens and specimen storage was completed during the fourth quarter of Year 1. Screening for this sub-project was opened on 8/20/08.

At the close of Year 2, 42 subjects had been enrolled in the study, with one screen-fail and one subject withdrawn. Eight of the 42 subjects expired due to their injuries. Preliminary analysis has focused on the first 30 cytokines subjects to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and outcome (Mortality, hospital length of stay, surgical management, 3 Month and 6 Month GOSE). At the close of Year 2 sufficient assay materials required for processing the first 30 study subjects were ordered.

Enrollment of the 50 subject target was completed in January 2010 and follow-up thru 1 year post injury was completed on all available subjects in Year 4 (January 2011). At the conclusion of the follow-up period, 10 (20%) of the 50 subjects had expired due to their injuries. Of those remaining, 38 subjects completed their 3 month follow-up, 36 completed their 6 month follow-up and 31 completed a 12 month follow-up interview. One subject declined further follow-up upon contact at 6 months, and two subjects were unable to be reached after multiple attempts.

During Year 3, remaining assay materials were acquired, analysis of serum samples for the first half of the study cohort was completed and initial processing of all CSF samples completed. At the close of Year 4, assays for all serum and CSF samples had been processed and analysis on the complete grouping was near completion. Detailed analysis on all data components and their relationship to specific outcome measurements had been initiated.

Analysis of the data set reached completion during Year 5, and all manuscripts related to this sub-project have been published in peer-reviewed journals.

Complete the Brain Resuscitation Registry network architecture

During Year 1, secure web-based trauma registry containing clinical patient information for trauma patients was established. Year 2 focused on the continuing development of the

network architecture. Links were established to automate the extraction of patient data needed to profile, enroll, manage and analyze current study populations. Study protocols were centralized and automated allowing for the establishment of communication between studies. Screens were added to the registry for current trauma patients to accommodate selection and clinical data management. The Cytokines sub-project served as the test study for these processes and for the training of research staff.

Year 3 progress included the installation of a dedicated server which, along with the purchase of dedicated screening tablets, allowed the implementation of a fully active automated screening process. Screening of all TRU Patients is now tracked through the system. Addition of a minimum required data feature ensures that key trauma data points are captured before the system will permit a patient to be closed out even if he/she is not suited for any study. Adjustments to the rules module (and its interface) were finalized so that it may accurately filter the required include/exclude criteria for the studies currently in the system.
The system restricts users on a study-by-study basis and can permit view only roles or other access restrictions based on the user's job responsibilities and study privileges. Reporting has continued to be developed. There are now real time screening statistics on each study that provide information on how many relevant patients were screened and the breakdown of why candidates were ineligible for a particular study.

Enhancements during Year 4 included security and workflow processes enhanced to allow a secondary screening phase if a study requires it. This permits study coordinators to distribute more intensive data collection responsibilities to specific users without holding up the patient in studies for which they have already been excluded. A dedicated interface is being installed between the main clinical information and the BRR. This will allow more autonomy and stability as it will not be dependent on ancillary systems for ADT data.

The outcomes survey process is now fully up and running allowing bi-weekly imports of completed outcome surveys. These surveys are administered on ScanTron forms that are then imported into the BRR and linked to the patients' initial screening and treatment data. The process has been enhanced to merge with the scheduling system so that the survey forms are pre-printed with the patient information prefilled out, thus making the visit matching process much more accurate and allowing for better auditing of staff compliance. Additionally, instant evaluation of the outcomes forms and coordination between the Shock Trauma clinic and rehab clinics is helping to aid in providing patients with immediate referrals for follow-up services.

A reporting database module is being developed that joins the three systems of the trauma registry, the Brain Resuscitation Server and the outcomes data. This will allow adhoc querying and data mining of anonymous case histories by researchers. It will also allow access of qualified users to full queries within the scope of their study protocols and regulations.
An intranet Wiki server has been set up allowing documentation of the Brain Resuscitation System for both technical and user personnel which permits easy online access to all help manuals.

During Year 5, the expansion of the registry to support a consistent and standardized approach to research efforts at the conclusion of this funding was continued. A reporting "Data Warehouse" that will receive admission and screening data and ultimately link to treatment information and follow-up data continues to evolve. Efforts have also been initiated to develop a returning patient notification module to monitor readmissions for previous study subjects. We

also continue to explore ways to stay current with technology and enhance workflow for the research screening and recruitment staff.

Retrospective Sub-projects

Two new retrospective sub-projects were initiated in Year 3, in preparation for prospective studies. Both were approved by UMB IRB as exempt protocols on 02/24/10 and approved as exempt by USAMRMC on 03/29/10

Traumatic Brain Injury and Fracture Fixation

Traumatic Brain Injury, Oxygenation and Outcomes

Traumatic Brain Injury and Fracture Fixation

The records for 167 consecutive TBI subjects with femoral shaft fractures between 06/2002 and 06/2009 were reviewed and analysis was completed. All patients with a head AIS > 2 who survived at least 12 hours beyond admission were included in the study.

One abstract based on these analyses has been presented and a manuscript has been submitted.

Traumatic Brain Injury, Oxygenation and Outcomes

Data for 1660 consecutive TBI subjects admitted between 06/2002 and 06/2009 were reviewed to identify predictors of outcome based on FiO2 delivery and analysis was completed.

Two abstracts have been presented based on this work and a manuscript was published

Sub-project 3: Animal Model of Brain Injury

The animal use protocol described in the initial statement of work was approved by the UMB IACUC on 9/21/07. It was subsequently submitted to the USAMRMC Animal Care and Use Review Office (ACURO) on 11/27/07. In response to the review by the USAMRMC ACURO, a revised protocol was submitted on 2/25/08 and approved by USAMRMC ACURO on 2/26/08.

During the course of Year 2, the model was changed to a large and small animal polytrauma model of contusional brain injury (controlled cortical impact) plus hemorrhagic shock. This change was necessary due to challenges in finding a vendor for the device necessary for conducting the penetrating brain injury paradigm with large animals, and feedback from the review of the last annual report that a large animal model of polytrauma caused by TBI plus hemorrhagic shock would be more clinically translational than that of a rodent model. A revised SOW was developed using a combination of both controlled cortical impact plus hemorrhagic shock with adult male Sprague Dawley rats and with adult male Hanford miniature swine (Sinclair Bio-resources).

In Year 3, the pig CCI model was finalized and approvals received by both UMSOM and ACURO. Development, equipment procurement and initiation of the two planned small and large animal model protocols proved more challenging than originally identified. Over Year 3 the original goal of developing a rat polytrauma model consisting of controlled cortical impact (CCI)-induced contusional brain injury plus hemorrhagic shock was reached. As expected the combination of hemorrhagic shock plus CCI results in death to cells in the cerebral cortex (cortical lesion

volume) that is significantly greater than that obtained with CCI alone. One consequence of hemorrhagic shock is a systemic inflammatory reaction that can result in multiple organ failure. While the degree of hypotension induced in our model is not sufficient to produce multiple organ failure, it is sufficient to induce systemic inflammation. We hypothesized that this reaction is responsible for the greater cortical lesion volume observed with the polytrauma model compared to that with CCI alone. At the end of Year 3 the CCI device for use in both the large and small animal models was purchased.

Mini-pig model

Year 4 efforts tested the above hypothesis through a series of directed experiments. During this period, we sought to establish a dose-response relationship between CCI impact depth and cortical lesion volume, using a large animal model consisting of mini-pigs. Progress on this aim was delayed by the difficulty in finding a company that would supply an appropriate CCI device and stereotaxic head-holder for pigs. The device was ordered late in Year 3 and was received during Year 4.

By the close of Year 4, the research team had successfully altered the degree of injury delivered with the new cortical impact device. While initial impact parameters were based on previously published data, experiments performed in our laboratory demonstrated that a cortical impact of 11 mm depth delivered at 5.0 m/s by our newly constructed CCI device results in a ruptured dura with herniated brain matter. In addition to widely evident subdural hemorrhaging, a depth of 11 mm results in widespread subarachnoid hemorrhaging on both the injured as well as the uninjured cerebral hemispheres (frontal, parietal, temporal and occipital) and cerebellum.

An impact depth of 7 mm delivered at 5.0 m/s resulted in a moderate injury where the dura was left intact with no herniation of brain matter. Although there was subdural hemorrhaging localized to the impact site on the ipsilateral hemisphere, there was no evidence of subdural hemorrhaging on the contralateral hemisphere and minimal bilateral subarachnoid hemorrhaging was contained to the cortical temporal and occipital lobes.

Activation of inflammatory processes and neuronal degeneration as evidenced by FJB positive cells, condensed chromatin, loss of NeuN immunoreactivity and axonal beading occurred within 4 hours following 7mm controlled cortical impact in the cavity penumbra as well as in the ipsilateral hippocampus.

Rat model

During late Year 4 and into Year 5, over 60 rat experiments with the device were completed. After many months of testing different variables, we have finalized the model to include a 1.25 mm depth of cortical impact followed by 30 min of hemorrhagic shock (mean arterial blood pressure (MABP) between 35 and 40 mm Hg. As a simulation of war fighter polytrauma in the field, rats are then provided pre-hospital resuscitation using HEXTEND injections to achieve MABP of 55-65 mm Hg over one hour. Animals then receive their shed blood at the beginning of their hospital-phase resuscitation and are slowly taken off isoflurane anesthesia one hour later.

The fixed brains were then stained with Fluoro Jade B (FJB) for determination of total cortical infarct volume, using stereologic analysis of 1 out of 24, or 6 sections per brain. The mean percentage of the total infarct plus cortical penumbra containing degenerating neurons is 22 ± 3 % (n = 6) for both hemispheres. Clearly, this polytrauma model produces severe TBI, but without significant mortality under these conditions. Based on the relatively consistent results

obtained with these pilot experiments we then completed randomized, blinded tests to determine if administration of sulforaphane, a drug found to be neuroprotective after CCI alone, is also neuroprotective for CCI plus hemorrhagic shock. Analysis of the results was completed during Year 5 and an abstract presented as well as a manuscript published based on the findings.

New sub-project: Transcranial Doppler and Brain Acoustic Monitoring

At the end of Year 3, a protocol to evaluate two non-invasive tools for assessment of cerebral perfusion and vasospasm in patients with severe TBI was developed. This protocol will use both Transcranial Doppler (TCD) screening and the Brain Acoustic Monitor (BAM) to study the incidence of vasospasm in patients with severe TBI. Using well-established criteria for vasospasm detected with TCD, the BAM device data will be analyzed to determine the ability to apply this non-invasive bedside tool to improve diagnostic capabilities in patients with severe TBI. Forty patients with severe TBI will be enrolled in this pilot study. Daily TCDs and BAMs will be obtained for 7 days following injury. Dr Kevin Sheth will be joining the research team as a co-investigator for this study. The protocol was initially approved by UMB IRB in March 2011, and requested USAMRMC HRPO modifications approved by UMB IRB in June 2011. USAMRMC requested UMB IRB determination for non-significant risk device, which was received on 12/05/11. And USAMRMC HRPO issued the approval memorandum on 12/19/11. At the time of continuing review with UMB IRB, modifications were required to bring the consent form in line with a new UMB template. These modifications were completed and approved on 03/12/12, and the continuing review was approved by UMB IRB on 03/14/12. The continuing review report was submitted to USAMRMC HRPO on 04/02/12 and the acceptance memorandum issued on 04/16/12.

This sub-project will initiate subject enrollment in October 2012 and subject follow-up and data analysis is projected to be completed by May 2014.

KEY RESEARCH ACCOMPLISHMENTS

Sub-project 1: Vital Signs Data in Trauma Patients

At the close of Year 1

- Enhanced the pre-flight patient Vital Signs data collection network
- Developed and expanded the in-trauma center VS data collection network to cover all critical care bays (TRU, OR, ICU)
- Developed and deployed a total pre and in-hospital VS data collection network
- Developed a basic VS data mining system to collect, process, and predict patient outcomes
- Established a road map for innovative prediction algorithm development

At the close of Year 2

- Completed the hospital/center based real-time patient physiological data collection network (covers all 90 trauma center beds)
- Developed a basic real time Shock Trauma Physiological (STP) Registry.

Key research findings include:

  - Continuous pre-hospital VS reviewed by 3 Subject Matter Experts (SME) identified more critical episodes (up to 300%) than Trauma Registry (TR).N=177
  - SME identified critical episodes (HR>120 bpm, SpO2<90, SBP<90mmHg) predicted outcome (mortality, length of stay, discharge GCS) better than TR. N=177.
  - Continuous pre-hospital VS better predicted emergency LSIs than TR (N=177)
  - EMS pre-hospital protocols may be monitored remotely in pre hospital care of TBI. (N=64)

At the close of Year 3

- Development of a computer assisted auto patient physiological (VS) data identification software, facilitating the successful matching of the 2008-2009 STC admission VS data for patients fitting enrollment criteria
- Continued development and refinement of continuous VS based prediction models
- Development of real-time ICU Team View (ICUTV), providing at-a-glance views of the 12 bed Neuro ICU VS trends

At the close of Year 3, a transition plan for the VS project was initiated. Information on the methods and strategies proposed to move the VS product to the next phase of development includes submission of a funding request to USAF to examine the Pulse Oximeter signal in more detail than is currently possible with infrastructure and equipment available under the current funding. In brief, the project seeks to identify, test and validate accuracy of algorithms, models and sensors to predict adverse events and the necessity for actionable therapeutic interventions including: hypoxemia, hemorrhagic shock, need for blood transfusion, chest tube insertion, airway management and other LSIs, and abdominal surgery to control hemorrhage.

At the close of Year 4

- Completion of case matching for 2010
- The project, titled “Continuous non-invasive monitoring and the development of predictive triage indices for outcome following trauma,” was funded by USAF (FA 8650-11-2-6D01); UM PI: Colin Mackenzie, USAF PI: Joseph J DuBose
- The project, titled “Traumatic Injury and Medical Evacuation – Patient Outcomes (TIME-PO), was funded by USAF ; USAF PI: David Power

At the conclusion of Year 5, the following fund was obtained or is anticipated as a result of preliminary work under this project

- For the project, titled "The Vitals Signs 'Genome Project'- Computational gene mapping to analyze continuous automated real-time vital signs monitoring data" was funded by USAF (MSA); UM PI: Deborah Stein
- The project, titled "Noninvasive intracranial pressure monitoring using advanced machine learning techniques" was funded by USAF; UM PI: Deborah Stein
- The project, titled "Fit to fly biomarkers after severe TBI" was funded by USAF (MSA); UM PI: Deborah Stein
- The project, titled "Predicting casualty blood product needs using pre-hospital vital signs" was submitted to USAFMSA and we are anticipating approval of funding in October 2012.

<u>Sub-project 2: Early Support of Intracranial Perfusion – Cytokines</u>

At the close of Year 2

- Recruitment of 42 study subjects

30 cytokines cases were used to study the relationship between the continuous patient VS (ICP, CPP, SBP, HR Variability and Pause Pressure Variability) and TBI patient outcome (Mortality, hospital length of stay, time of craniotomy, 3 Month, 6 Month and 12 month GOSE). The findings are

  - ICU ICP>20, 30 CPP<50<60 predicts patient outcome better than patient charts VS.
  - Combined ICP>20 and CPP<60 episodes predict outcome better than individual ICP and CPP.
  - Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI.
  - The "Brain Trauma Index": Dynamic 3-D scoring in the assessment of TBI
  - Computerized patient vital signs charting method enhances real-time record keeping in ICU
  - Heart rate variability is associated with intractable intracranial hypertension and cerebral hypoperfusion

At the close of Year 3

- Recruitment of targeted 50 subjects
- Preliminary processing of serum and CSF samples for all subjects
- Analysis of all samples and correlation to clinical markers of TBI severity
- Determination of serum and CSF biomarkers that predict worsening of cerebral hypoperfusion, intracranial hypertension, and cerebral hypoxia.

At the close of Year 4

- Data collection and longitudinal follow-up was completed
- Processing of serum and CSF samples was completed

At the close of Year 5

- Detailed analysis of all data points was complete, and as well as final manuscript preparation and submission

Sub-projects – Retrospective

TBI and Fracture Fixation

At the close of year 3, preliminary analysis completed, key findings include:

- Early femur fracture fixation in TBI subjects correlates with significantly reduced hospital and ICU length of stay
- Early definitive fracture stabilization has no detrimental effect on mortality and discharge GCS
- 1 abstract had been presented

At the close of Year 5

- 1 manuscript had been submitted for publication

TBI, Oxygenation and Outcomes

At the close of year 3, preliminary analysis nearing completion, early key findings include:

  - Hyperoxemia within the first 24 hours of hospitalization increases mortality and worsens short-term functional outcomes in TBI subjects.
  - Poor outcomes may be predicted by hypoxia within the first 24 hours of admission

At the close of Year 4,

- 1 abstract had been presented

At the close of Year 5,

- 1 additional abstract had been presented and 1 manuscript published

Sub-project 3: Animal Model of Brain Injury

At the close of Year 2

- A rat polytrauma model consisting of controlled cortical impact traumatic brain injury plus hemorrhagic shock had been successfully developed.
- Preliminary experiments performed with human cerebrospinal fluid samples indicate that they can be used in a new and novel assay that detects toxicity of these samples on culture cell lines, using cellular respiration and glycolysis as outcome measures

At the close of Year 3,

- Rat model for CCI plus hemorrhagic shock was finalized
- CCI device for both rat and mini-pig models was purchased

At the close of Year 4,

- Initiation of rat CCI model
- Initiation of mini-pig CCI model

At the close of Year 5,

- Rat and mini-pig CCI models had been completed including data analysis
- 1 abstract had been presented and 1 manuscript published based on the findings.

REPORTABLE OUTCOMES

a) Presentations:

5th Annual Innovations in the Surgical Environment Conference, June, 2008

Lesson learned: developing in-fight patient vital-signs data collection network
Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C, and Trauma Vital Signs Investigator and Associates (TVSI,TVSRA) Group

Can pre-hospital patient VS predict injury and intervention?
Hu P, Mackenzie C, Dutton R, Sen A, Floccare D, Bochicchio G, Xiao Y, Spearman J, Scalea T.

Challenges in developing real-time patient vital sign data collection network for trauma care. Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Telemedicine Association Annual meeting, April, 2008

Challenges in developing real-time in-flight patient vital-signs data collection system.
Hu P, Handley C, Seebode S, Conway A, Gens R, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D.

Real-time Patient Vital Sign Data Collection Network for Trauma Care.
Hu P, Mackenzie C, Dutton R, Bochicchio G, Bochicchio K, Xiao Y, Spearman J, Scalea T.

American Society of Anesthesiologists Annual Conference, October, 2008

Continuous prehospital vital signs record identifies increased abnormalities/predicts interventions. Sen A, Hu P, Mackenzie C, Jordan S, Dutton R.

Correlation between ECG heart rate and pulse oximeter heart rate in prehospital aeromedical trauma transfer. Sen A, Hu P, Dutton RP, Mackenzie CF, Alexander M, Xiao Y.

American Medical Informatics Association Annual Symposium November, 2008

Automatic pre-Hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps. Mackenzie C, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T.

Statewide real-time in-flight trauma patient vital signs collection system. Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Handley C, Ho D, Scalea T.

American Telemedicine Association Conference, April, 2009

Automated vital-sign recording identifies more critical episodes than chart abstraction. Hu P, Sen Y, Mackenzie C, Xiao Y, Jordan S, Dutton R, Scalea T, and Trauma Vital Signs Research Group (TVSG)

Can EMS protocols be monitored remotely in pre hospital care of traumatic brain injury (TBI)? Mackenzie C, Hu P, Sen A, Xiao Y, Jordan S, Dutton R, Scalea T.

16th World Congress of Disaster and Emergency Medicine, May, 2009

Continuous vital signs acquisition improves prehospital trauma triage. Sen A, Hu P, Mackenzie C, Jordan S, Xiao Y, Dutton R, Scalea T

In-flight vital signs blackbox for trauma care. Hu P, Mackenzie C, Dutton R, Sen Y, Xiao Y, Floccare D, Scalea T.

Video technologies in emergency health research in assessing quality of care: a study of trauma resuscitation milestones. Sen A, Hu P, Mackenzie C, Xiao Y, Dutton R.

American Association for the Surgery of Trauma AAST 2009 Annual Meeting, October, 2009

Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T.

American Society of Anesthesiologists ASA2009 Annual Meeting October, 2009

Real-time patient vital signs data registry for trauma patient care. Dutton R, Hu P, Xiao Y, Yeatts D, Mackenzie C.

High resolution ICP and CPP data better predict outcome of severe TBI. Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T.

American Medical Informatics Association AMIA 2009 Annual Meeting November, 2009

CPP/ICP dose index: Dynamic 3-D scoring in the assessment of TBI. Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T.

Computerized patient vital signs charting method enhances real-time record keeping in ICU. Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y.

Is there added value in continuous vital signs and video collection linked to trauma patient outcomes? Hu P, Mackenzie CF, Xiao Y, Seebode D, Wong M, Murdock K, Dutton R.

Society for Critical Care Medicine's 39th Critical Care Congress January, 2010

Heart rate variation is associated with intractable intracranial hypertension and cerebral hypoperfusion. Kahraman S, Dutton R, Hu P, Stansbury L, Xiao Y, Stein D, Scalea T .

Critical care monitoring in the field: Pre-hospital continuous vital signs acquisition identifies best predictors of life-saving interventions in trauma patients. Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T.

Cerebrospinal fluid levels of inflammatory mediators: association with outcome following severe traumatic brain injury. Stein DM, Murdock KR, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

Eastern Association for the Surgery of Trauma (EAST) 23rd Annual Scientific Assembly, January 2010

CSF levels of NSE and S100B in patients with severe TBI: correlation with clinical measures. Stein DM, Murdock KR, Kufera JA, Menaker J, Bochicchio GV, Dutton RP, Aarabi B, Scalea TM.

6th Innovations in the Surgical Environment Conference March, 2010

Trauma center wide real-time patient vital signs data registry (VSDR) for improvement of patient safety. Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T.

International Society for Magnetic Resonance in Medicine, May, 2010

Early diffusion changes following controlled cortical impact injury on a rat model. Zhuo J, Xu S, Racz J, Fiskum G, Gullapalli R.

Early metabolic changes following focal traumatic brain injury in rats measured using 1H MRS. Xu S, Roys S, Racz J, Shi D, Zhou J, Gullapalli R, Fiskum G.

2010 American Telemedicine Association Annual International Meeting May, 2010

High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes. Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T.

Association of University Anesthesiologists, Annual Meeting, May 2010

New uses of vital signs signals during resuscitation to triage, assess provider performance and predict outcomes.
Mackenzie CF, Hu PF, Ayan S, Woodford M, Floccare D, Scalea T.

NNS 2010: 28th Annual National Neurotrauma Symposium, June 2010

Early hypotension redefined in patients with severe TBI. Stein, DN, Brenner M, Sheth K, Hu P, Aarabi B, Scalea T.

Early fracture fixation improves select outcomes in TBI patients.
Brenner M, Stein DM, Hu P, Scalea T

8th Annual Neurocritical Care Society Meeting, September 2010

Association of CSF biomarkers and secondary insults following severe traumatic brain injury. Stein D, Kufera J, Lindell A, Murdock KR, Menaker J, Bochicchio GV, Aarabi B, Scalea TM.

Depth and duration of secondary insults predicts outcome in patients with severe traumatic brain injury. Stein D, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM

American Association for the Surgery of Trauma (AAST 2010) Annual Meeting, September 2010

Relationship of serum biomarkers to depth and duration of secondary insults following severe TBI.
Stein D, Lindell A, Murdock K, Menaker J, Keledjian K, Bochicchio G, Scalea T.

Dynamic three-dimensional scoring of cerebral perfusion pressure and intracranial pressure provides a Brain Trauma Index that predicts outcome in patients with severe TBI.
Kahraman S, Dutton R, Hu P, Stansbury L, Hess J, Xiao Y, Stein D, Scalea T.

American Society of Anesthesiologists Annual Scientific Meeting. October 2010

Continuously recorded SPO2 outperforms SPO2 from trauma registry in prediction of mortality. Woodford M, Mackenzie CF, Hu P, Dutton R, Scalea T.

Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients. Grissom T, Hu P, Dubose J, Dutton R, Stein D.

American Medical Informatics Association Annual Symposium, November, 2010

Using vital signs network to improve patient safety: How many alarms are too many?
Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y.

Eastern Association for the Surgery of Trauma (EAST) 24th Annual Scientific Assembly, January, 2011

Brief episodes of intracranial hypertension and cerebral hypoperfusion are associated with poor functional outcome following severe traumatic brain injury. Stein D, Hu PF, Brenner M, Sheth K, Aarabi B, Scalea TM.

Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

Traditional Systolic Blood Pressure Targets Underestimate Hypotension-induced Secondary Brain Injury. Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM

American Telemedicine Association Annual Meeting 2011

Pre-hospital hypoxemia and tachycardia trends better predict patient mortality than Trauma Registry values Hu P, Woodford M, Mackenzie CF, Dutton R, Seebode S, Liu K, Scalea T.

Brief Episodes of Abnormal Shock Index Predicts Mortality in Severe Traumatic Brain Injury. Hu P, Stein DM, Stansbury L, Brenner M, Kufera J, Xiong W, Jiao X, Scalea T.

Association of University Anesthesiologists Annual Meeting 2011

Real- time decision support during trauma patient resuscitation. Mackenzie CF, Hu PF, Stein D, DuBose J, Grissom T.

National Neurotrauma Society Symposium July 2011

Use of serum biomarkers to predict cerebral hypoperfusion following severe traumatic brain injury. Stein DM, Lindell A, Murdock K, Kufera J, Menaker J, Bochicchio G, Aarabi B, Scalea T.

Eastern Association for the Surgery of Trauma (EAST) Jan, 2012 conference

Computational Gene-Mapping to Analyze Continuous Automated Physiologic Monitoring data in Neuro-trauma Intensive Care. Stein D, Stansbury L, Hu P, Chang, Scalea T.

Pacific Coast Surgical Association, February 2012

Early hyperoxia worsens outcomes after traumatic brain injury (TBI). Brenner M, Stein D, Hu P, Kufera J, Woodford M, Scalea T.

National Capital Area TBI Symposium. Bethesda, May 2012

Hyperoxic versus normoxic resuscitation in a rat polytrauma model of TBI plus hemorrhage shock. Proctor, JL, Pan Y, Gupta E, Bordt E, Fiskum, G.

International Conference on Machine learning and Data Mining MLDM 2012, Berlin, July 2012

Outcome prediction for patients with severe traumatic brain injury using permutation entropy analysis of electronic vital signs data. Kalpakis K, Yang S, Hu P, Mackenzie C, Stansbury L, Stein D, Scalea T.

Neurotrauma 2012 Symposium, Phoenix, AZ, July 2012

Timing of Secondary Insults Following Severe Traumatic Brain Injury. Stein DM, Brenner M, Hu P, Zhu XS, Stansbury LG, Aarabi B, Scalea TM.

25th IPPR Conference on Computer Vision, Graphics and Image Processing, Taiwan, August 2012

Utility of 3-Dimensional ROC in using vital signs signal for blood transfusion. Chang CI, Hu P, Chen SY, Mackenzie C, Stansbury L, DuBose J, Scalea T

Military Health System Research Symposium (MHSRS) / ATACCC, Aug 2012

How Can We Reduce Transient Monitor Alarms in Trauma Resuscitation Units? Hu P, Chiu W, Mackenzie C, Miller C, Fang R, Xiong W, Hu E, Stein D, Scalea T.

American Association for the Surgery of Trauma (AAST) Annual Conference, September 2012
Timing of Intracranial Hypertension Following Severe Traumatic Brain Injury.
Stein DM, Brenner M, Hu PF, Stansbury L, Aarabi B, Scalea T.

b) Publications (Journal or Proceedings):

Proceedings – abstracts and full length articles

Mackenzie CF, Hu P, Sen A, Dutton R, Seebode S, Floccare D, Scalea T. **Automatic pre-hospital vital signs waveform and trend data capture fills quality management, triage and outcome prediction gaps.** AMIA Annu Symp Proc. Nov 6:318-22, 2008

Hu PF, Handley C, Seebode S, Conway A, Gens Y, Mackenzie C, Ho D, Defouw G, Davies P, Floccare D. **Challenges in Developing Real-Time In-Flight Patient Vital-Signs Data Collection System**. Telemedicine and e-Health. 14(1)105, 2008

Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T. **Real-time Patient Vital Sign Data Collection Network for Trauma Care** . Telemedicine and e-Health. 14(1)62, 2008

Hu P, Handley C, Sen A, Seebode S, Conway A, Gens R, Kramer B, Jordan S, Webb R, Defouw G, Davies P, Ho D, Xiao Y, Mackenzie C **Lesson Learned: Developing In-Flight Patient Vital-Signs Data Collection Network** Proceedings of 5th Annual Innovations in the Surgical Environment Conference, 2008

Hu PF, Mackenzie CF, Dutton R, Bochicchio GV, Bochicchio K, Xiao Y, Spearman J, Scalea T. **Challenges in developing real-time Patient Vital Sign Data Collection Network for Trauma Care** . Proceeding of 5th Annual Innovations in the Surgical Environment Conference. 2008

Sen A, Hu P, Dutton RP, Mackenzie CF, Alexander M, Xiao Y,. **Correlation between ECG Heart rate and Pulse Oximeter Heart rate in Prehospital aeromedical trauma transfer** Proceedings of the American Society of Anesthesiologists. 2008 .

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Sen A, Hu P, Mackenzie C, Jordan S, Dutton R. **Continuous Prehospital Vital Signs Record Identifies Increased Abnormalities/Predicts Interventions**. Proceedings of the American Anesthesiologists Annual Conference A1637. 2008

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Kahraman S, Hu P, Xiao Y, Dutton R, Aarabi B, Stein D, Scalea T. **Pressure-time dose of automated ICP and CPP data predicts outcomes in severe TBI** . Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference, 2009

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Dutton R, Kahraman S, Hu P, Xiao Y, Scalea T. **High resolution ICP and CPP data better predict outcome of severe TBI**. Proceedings of the American Society of Anesthesiologists Annual Conference A451154, 2009

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Kahraman S, Hu P, Xiao Y, Dutton R, Stein D, Scalea T. **CPP/ICP Dose Index: Dynamic 3-D Scoring in the Assessment of TBI.** Proceedings of the American Medical Informatics Association AMIA-0061-A2009, 2009

Hu P, Akozer S, Lindell A, Liu K, Mitrou M, Gettings L, Stein D, Xiao Y. **Computerized patient vital signs charting method enhances real-time record keeping in ICU**. Proceedings of the American Medical Informatics Association - AMIA-0060-A2009, 2009

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Hu P, Mackenzie C, Dutton R, Sen A, Xiao Y, Floccare D, Scalea T. **In-flight Vital Signs Blackbox for Trauma Care**. Prehospital and Disaster Medicine 24(2):s52-s53. 2009

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Sen A, Hu P, Mackenzie C, Dutton R, Jordan S, Xiao Y, Scalea T. **Critical Care Monitoring in the Field: Pre-Hospital Continuous Vital Signs Acquisition Identifies Best Predictors of Life-Saving Interventions in Trauma Patients.** Proceedings of The Society of Critical Care Medicine (SCCM) p.A329, 2010

Hu P, Stein D, Xiao Y, Dutton R, Kahraman S, Yeatts D, Grissom T, Mackenzie C, Scalea T. **Trauma Center Wide Real-time Patient Vital Signs Data Registry (VSDR) for Improvement of Patient Safety** Proceedings of the 6th Innovations in the Surgical Environment Conference, 2010

Woodford M, Mackenzie CF, Hu P, Dutton R, Scalea T. **Continuously recorded SPO2 outperforms SPO2 from trauma registry in prediction of mortality.** Proceedings of American Society of Anesthesiologists Annual Scientific Meeting, 2010

Hu P, Akozer S, Dutton R, Stein D, Murdock K, Xiao Y, Scalea T. **High frequency ICU perfusion pressure critical episodes predicts TBI patient outcomes** Proceedings of the American Telemedicine Association Annual Conference, May 2010

Stein DM, Hu P, Kahraman S, Brenner M, Sheth K, Aarabi B, Scalea TM. **Depth and Duration of Secondary Insults Predicts Outcome in Patients with Severe Traumatic Brain Injury.** Proceedings of Neurocritical Care Society Meeting, September 2010

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Brenner M, Stein D, Hu P, Kufera J, Scalea T. **Early Fracture Fixation Improves Select Outcomes in Traumatic Brain Injury Patients** Proceedings of 28th Annual National Neurotrauma Society Symposium June 14-17, 2010

Grissom T, Hu P, Dubose J, Dutton R, Stein D**. Failure to achieve normothermia is not associated with worsened outcomes in brain injury patients.** Proceedings of American Society of Anesthesiologists Annual Scientific Meeting, 2010

Hu P, Mackenzie C, Stein D, Chang W, Seebode S, Binder M, Kramer ME, Xiao Y. **Using vital signs network to improve patient safety: How many alarms are too many?** Proceedings of American Medical Informatics Association Annual Symposium, 2010

Kahraman S, Dutton R, Hu P, Stansbury L, XiaoY, Stein D, Hess J, Scalea T. **Cerebral perfusion pressure/intracranial pressure dose index: Dynamic 3-D scoring in the assessment of Traumatic Brain Injury** Proceedings of American Association for the Surgery of Trauma (AAST) Annual Conference. September 2010

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Proceedings of Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly
M Brenner, D Stein, P Hu, J Kufera, M Wooford, T Scalea **Too much of a good thing? Early hyperoxemia worsens outcomes in TBI patients** Proceedings of Western Association for the Surgery of Trauma (WEST) 2011 Annual Scientific Assembly

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Mackenzie C, Hu F, Stein D, DuBose J, Grissom T. **Real- time decision support during trauma patient resuscitation** Proceedings of a Association of University Anesthesiologists 2011

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Journals

Kahraman S, Dutton RP, Hu P, Xiao Y, Aarabi B, Stein DM, Scalea TM **Automated Measurement of "Pressure Times Time Dose" of Intracranial Hypertension Best Predicts Outcome After Severe Traumatic Brain Injury.** Journal of Trauma 2010; 69(1):110-118.

Kahraman S, Stansbury L, Hu P, Xiao Y, Stein DM, Scalea TM. **Heart rate and pulse pressure variability are associated with intractable intracranial hypertension after severe traumatic brain injury.** Journal of Neurosurgical Anesthesiology 2010; 22(4):296-302.

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Woodford MR, Mackenzie CF, DuBose J, Hu P, Kufera J, Hu E, Dutton RP, Scalea TM. **Continuously Recorded SpO2 and Heart Rate During Pre-Hospital Transport Outperform Initial Measurement in Prediction of Mortality after Trauma.** J Trauma Acute Care Surg. 2012 Apr;72(4):1006-12.

Brenner M, Stein DM, Hu PF, Aarabi B, Sheth K, Scalea TM **Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury** J Trauma. 2012 May;72(5):1135-9

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CONCLUSIONS

At the conclusion of Year 5 significant progress has been made toward meeting overall project milestones. The infrastructure of staff, technology and data management to support the completion of sub-projects and long-term assessment of TBI patients had been created. The robust Brain Resuscitation Registry (BRR) needed to accomplish the goals of this multi-year project has been implemented and continues to undergo refinement especially in terms of reporting. Recruitment and data collection for the Vital Signs human sub-projects are completed and data analysis and prediction model development are complete for this project. New funding has been pursued to continue the efforts. Sub-project 2, Cytokines has completed subject recruitment and follow-up, specimen processing and data analysis. Both animal sub-projects have been completed and analysis finalized. Two retrospective human sub-projects have been completed and manuscripts submitted and/or published detailing the results. The protocol for the final new human use sub-project has been approved and the multiple challenges associated with initiating this project managed. Subject enrollment, data collection and analysis will be the sole focus of the final 20 month no-cost extension to conclude in May 2014.

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APPENDICES

Abstracts Accepted or Presented since last Annual Report

Computational Gene-mapping to Analyze Continuous Automated Physiologic Monitoring Data in Neuro-Trauma Intensive Care

Stein D, Stansbury LG, Hu P, Chen H, Scalea TM

Objectives: Neuro-trauma (NT) ICU-monitor electronic signal data can be processed into sequences analogous to amino acid sequences in genes. We asked whether high-information throughput applications used in micro-array gene profiling can assess critical thresholds in large volume collections of continuous electronic automated physiologic monitoring data, with the eventual goal of establishing critical thresholds specifically relevant to the individual patient.

Methods: We used Class Prediction Analysis, a structured learning technique, to predict binary outcomes (survival, yes/no; 14-day hospital or ICU Length of Stay [LOS]; good/bad Extended Glasgow Outcome Score [GOSE] at 3 months) based on data accrued over 12, 24, 48, and 72 h after admission to the NT ICU. We then used univariate analysis 'feature selection' to identify discriminator 'genes' in each individual's data set. Prediction models using each individual's 'featured' genes were then constructed using 7 different statistical modeling techniques to predict outcome for other individuals in the sample cohort based on the selected 'features' of each individual, using 'leave one out' methodology.

Results: Sixty patients with severe traumatic brain injury (TBI) provided 56 sets of 588 'genes' for each of the 4 periods and outcomes. Mean number (SD) of 'featured' genes ranged from 96(14) predicting 14-day hospital stay by 12 h to 5(1) predicting 3-month GOSE by 12 h. 'Genes' predicting mortality ranged progressively from 13(1) at 12 hours to 51(5) at 72 h. Cerebral and blood pressures over time (e.g. intracranial pressure >20 mmHg for 20 min) provided the best discrimination for outcome, with blood pressure indicators more prominent at 12 and 24 hours and cerebral pressure indicators, sometimes for as little as 10 min, more prominent at 48 and 72 hours. Four of the 7 modeling techniques constructed models that correctly identified outcomes =75% of the time. Over all, modeling performed best for mortality and worst for GOSE at 3 months.

Conclusion: Our results suggest that valid prediction models after severe TBI can be constructed using 'gene mapping' techniques to analyze large datasets from conventional electronic monitoring data, but that this methodology needs validation in larger data sets

Hyperoxic Versus Normoxic Resuscitation in a Rat Polytrauma Model of TBI Plus Hemorrhagic

Proctor JL, Pan Y, Gupta E, Bordt E, Fiskum G

INTRODUCTION: Many civilian and warfighter TBI victims experience additional injuries, including those that result in hemorrhagic shock (HS). Reduced O2 delivery that accompanies HS may exacerbate TBI. Thus, use of inspired or ventilator O2 might overcome reduced O2 delivery and improve neurologic outcome. This project developed a rat polytrauma model consisting of contusional cortical brain injury followed by moderate hemorrhagic shock and then fluid and blood infusion resuscitation phases. This study tested the hypothesis that inspiration of 100% O2 during these resuscitation phases reduces brain lesion volume compared to that observed in the absence of supplemental O2.

METHODS: A femoral artery catheter was placed in isoflurane anesthetized rats and brain injury was induced by controlled cortical impact (CCI) at a depth of 1.25 mm, a velocity of 4.8 m/s and duration of 50 msec. HS was then induced by removal of blood in a decelerating fashion through the arterial catheter until the target range of 38 - 40 mm Hg for mean arterial pressure was reached. This shock level was maintained for 30 min and then followed by a one hr "Pre-Hospital" fluid resuscitation phase utilizing infusion of Hextend (6% hetastarch in lactated ringer solution). This period was followed by a one hr "Hospital Phase" when shed blood was returned to rats at an infusion rate of 1 ml/min. Rats used in these experiments were randomized to 4 groups: A. Sham Normoxic. B. Sham Hyperoxic. C. Polytrauma Normoxic. Polytrauma Hyperoxic. Sham rats were anesthetized and underwent a craniotomy but no cortical impact and no HS. Polytrauma rats inspired either room air (Normoxic) or 100% O2 (Hyperoxic) for both the Pre-Hospital and Hospital resuscitation phases. At the end of the 2 hr period of O2 inspiration, the arterial O2 tensions was 401 ± 25 mm Hg compared to 73 ± 1 mm Hg for rats breathing room air. Rats were perfused with fixative at 30 day post injury. Seven brain sections (40 μm thick, 960 μm apart), corresponding to the epicenter of CCI induced cortical injury, 3 sections rostral and 3 sections caudal to that section, were stained with Fluorojade B (FJB) and used for stereology-based quantification to estimate lesion and damaged cortical volume.

RESULTS: Cortical region volumes in the ipsilateral hemisphere were classified as contusion (necrotic divot) or penumbral (FJB positive) regions and were separately quantified using unbiased stereologic methods. Overall lesion volume is defined as contusion + penumbral volumes (mm3) in the ipsilateral cortex. This study was powered at ten rats per treatment group. At this time, brains from a total of n=4 Sham CCI + HS, n=8 Normoxic, and n=5 Hyperoxic Polytrauma rats have been quantified. Preliminary results indicate that although there is a difference in overall lesion volume between Sham groups (1.90 ± 0.63, n=4) and both Polytrauma Normoxic (12.03 ± 2.47, n=8) and Polytrauma Hyperoxic (8.68 ± 1.52, n=5) groups, there is no difference in overall lesion volume between Normoxic and Hyperoxic Polytrauma groups. There is also no apparent difference between the penumbral volumes for Normoxic (7.48 ± 1.16) and Hyperoxic (7.30 ± 1.61) Polytrauma groups. There is an apparent sparing of the necrotic volume, however, for Hyperoxic (1.37 ± 0.31) compared to Normoxic (4.5 ± 1.80) resuscitated animals.

CONCLUSIONS: A combat-relevant rat polytrauma model was developed that combines TBI caused by controlled cortical contusion with a moderate period of hemorrhagic shock. This model includes a pre-hospital fluid resuscitation phase followed by a hospital phase when normal blood pressure is reached by infusion of shed blood. No definitive conclusions about the effects of Normoxic compared to Hyperoxic resuscitation on neuropathologic outcome can be made until the lesion volumes for all brains have been quantified. Our current speculation is that Hyperoxic resuscitation may reduce the contusion volume but not the overall lesion consisting of contusion plus penumbral volumes. The final outcomes from this study may support the use of hyperoxic resuscitation for victims of TBI/polytrauma, including injured warfighters.

ACKNOWLEDGEMENTS: This work was supported by USAMRMC Awards W81XWH-09-2-0187 and W81XWH-07-2-0118

Early Hyperoxia Worsens Outcomes After Traumatic Brain Injury

Brenner M, Stein DM, Hu P, Kufera J, Woodford M, Scalea T

Objectives: Hypoxia worsens outcomes in TBI patients, however, little is known about the effects of other oxygen levels. We investigated the relationship between oxygenation and short-term outcomes in TBI patients.

Design: Logistic regression analysis was used to determine whether average high (> 200 mmHg) or low (<100 mmHg) PaO2 levels within the first 24 hours of admission correlated with patient outcomes relative to patients with average PaO2 levels between 100 and 200 mmHg.

Patients: We retrospectively reviewed 1558 consecutive severe TBI patients who survived past 12 hours after admission.

Main Outcome Measures: We measured mortality, ICU length of stay (ICULOS), hospital length of stay (HLOS), and discharge Glasgow Coma Scale (DCGCS).

Results: 77% were male and 89% sustained blunt trauma. Mean age, admission GCS, and Injury Severity Score (ISS) were 41.3 ±20.6 years, 8.3 ±4.7, and 31.9 ±12.5. ICULOS and HLOS were 8.7 ±10.5 and 13.8 ±13.7 days. Average DCGCS was 10.1 ±4.7. Mortality rate was 28%. After controlling for age, gender, ISS, mechanism of injury, and admission GCS, patients with high PaO2 levels had significantly higher mortality, and lower DCGCS patients with a normal PaO2 ($p<0.05$). Patients with low PaO2 levels also had increased mortality ($p<0.05$).

Conclusion: Hyperoxia within the first 24 hours of hospitalization is associated with worse short-term functional outcomes and is associated with higher mortality after TBI. Although the mechanism for this has not been completely elucidated, it may involve hyperoxia induced oxygen free radical toxicity with or without vasoconstriction. Hyperoxia and hypoxia were found to be equally detrimental to short-term outcomes in TBI patients. A narrower therapeutic window for oxygenation may improve mortality and functional outcomes.

Outcome prediction for patients with severe traumatic brain injury using permutation entropy analysis of electronic vital signs data

Kalpakis K, Yang S, Hu P, Mackenzie C, Stansbury L, Stein D, Scalea T.

Abstract.

Permutation entropy is computationally efficient, robust to noise, and effective to measure complexity. We used this technique to quantify the complexity of continuous vital signs recorded from patients with traumatic brain injury (TBI). Using permutation entropy calculated from early vital signs (initial 10_20% of patient hospital stay time), we built classifiers to predict in-hospital mortality, and mobility measured by 3-month Extended Glasgow Outcome Score (GOSE). Sixty patients with severe TBI produced a skewed dataset that we evaluated for accuracy, sensitivity and specificity. With early vital signs data, the overall pre-diction accuracy achieved 91.67% for mortality, and 76.67% for 3-month GOSE in testing datasets, using the leave-one-out cross validation. We also applied Receiver Operating Characteristic analysis to compare classifiers built from different learning methods. Those results support the applicability of permutation entropy in analyzing the dynamic behavior of biomedical time series for early prediction of mortality and long-term patient outcomes

Timing of Secondary Insults following Severe Traumatic Brain Injury

Stein DM, Brenner M, Hu PF, Zhu XS, Stansbury LG, Aarabi B, Scalea TM

Objectives: Intracranial hypertension (ICH) and cerebral hypoperfusion (CH) worsen outcome after severe traumatic brain injury (sTBI). There is little objective data that describe when these occur. We objectively evaluated the timing of ICH and CH to see if there were temporal differences in patients with good vs. poor outcome.

Methods: Patients with head AIS≥3, age>14 years, and need for intracranial pressure (ICP) monitoring were prospectively enrolled over 2 years. Continuous, automated, digital data was collected every 6 seconds and 5 minute means were calculated for the duration of monitoring. ICP and Cerebral Perfusion Pressure (CPP) were captured over 12-hour time periods from admission through hospital day 7. The Brain Trauma Index (BTI=CPP/ICP) was calculated for these time periods. Outcome was measured by Extended Glasgow Outcome Scale (GOSE) or dichotomized functional evaluations at least 3 months after injury.

Results: 207 patients were enrolled. Mean age was 39 years (range 16-84), mean admission GCS 6.8 ±3.6, mean head AIS 4.3 ±0.7, and mean Marshall score 2.6 ±0.8. The in-hospital mortality was 21.7%, with 29 (14%) dying from sTBI. Of the 162 survivors, 123 had functional evaluations. 95 had good functional outcome (77%). Lowest mean BTI occurred hours 12-24 (9.0) and hours 132-144 (8.9) after admission. When stratified by functional outcome, survivors demonstrated dramatically different temporal patterns of ICP increases and CPP decreases as measured by BTI, with the first 72 hours being nearly indistinguishable between the 2 groups.

Conclusion: Early in the hospital course, secondary insults occur frequently. Patterns of ICP elevation and CPP decline, as measured by the BTI, are the same in the first 3 days but then differ significantly based on functional outcome. Understanding the temporal nature of secondary insults has significant implications into developing more evidenced-based management approaches.

Utility of 3-Dimensional ROC in using Vital Signs Signals for Blood Transfusion Decision Assistance

Chang CI, Hu P, Chen SY, Mackenzie C, Stansbury L, DuBose J, Scalea T

Abstract:

3D Receiver operating characteristic (ROC) analysis has recently received considerable interest in a wide range of applications in signal processing and medical diagnosis. It introduces a threshold parameter as an additional 3rd dimension to account for multiple decisions rather than a single decision generally used by 2D ROC analysis. This paper presents a new application of 3D ROC analysis to assist decision-making for trauma patient using vital signs (VS) such as heart rate (HR), systolic blood pressure (SBP) to predict the need for immediate blood transfusion upon arrival at advanced trauma care. The utility of 3D ROC analysis enables multiple decisions using various threshold values of continuous VS data. This 3D ROC analysis provides users with an analytic and effective platform to evaluate adjustable sensitivity and specificity resulting from multiple decisions for clinical decision-assist tools.

How Can We Reduce Transient Monitor Alarms in Trauma Resuscitation Units?

Hu PF, Chiu W, Mackenzie C, Miller C, Fang R, Xiong W, Hu EZ, Stein D, Scalea T

Purpose: To analyze the frequency and the duration of different categories of patient monitor alarms and to assess their effectiveness of impacting the care patients of varying severity in a trauma resuscitation unit (TRU).
Design: Retrospective analysis
Population: One year of TRU patient admissions to a major trauma center
Methods: In 2009, 7,800 patients were admitted to the 12 TRU bays in a major trauma center. The status of all TRU vital signs (VS) monitor alarms was recorded from the networked patient VS monitors (GE Solar). The alarms were grouped into four categories: Patient Crisis, Patient Warning, Patient Advisory, and System Warning. Trauma patients were subdivided according to their criticality based on their admission Glasgow Coma Scale (GCS) <=8 (more critical) or GCS> 8 (less critical) .
Data Analysis: Trauma patient criticality was correlated with the four alarm categories. The alarm frequency, duration, and percentages of alarms <5 or <10 seconds were calculated within the four alarm categories.
Findings: In a 12 month period, a total of 316,688 alarms were recorded for 6,701 (501 GCS<=8) admitted trauma patients. Only 7,694 (3%) of alarms warned of Patient Crisis, the remaining alarms were 37% Patient Warning, 45% Patient Advisory, and 15% System Warning. 25% of all alarms were < 2 seconds in duration, and 50% of alarms were <5 seconds. The GCS<=8 subgroup had an average of 12 alarms per hour, while the GCS>8 subgroup averaged 6.6 alarms per hour. 35% and 47% of Patient Crisis alarms were < 5 and <10 seconds respectively. For GCS<=8 patients, the top three reasons for alarms were Check Adapter (22%), Tachy (10%) and SPO2 Low (6%). Among the System Warning alarm category, the top three reasons for alarms were Leads Failures (26%), Respiratory Rate Leads Failure (25%) and SpO2 Probe Failure (21%).
Conclusion: 97% of alarms were not found to be Patient Crisis alarms. The median duration of alarms was 5 seconds, suggesting that the majority of alarms were transient in nature. During provider multi-tasking associated with trauma patient resuscitation, managing non-patient related clinical monitoring alarms is an unwanted distraction. Repetitive non-critical alarms also potentially increase the threshold for response to true Patient Crisis alarms.
Implications: Patient safety may be improved by refining alarm management practices, such as using technology to filter out spurious alarms and improving system technology to minimize sensor disconnects. Our study suggests that a straightforward method that could avoid 25 to 50% of transient alarms would be to introduce a 2 to 5-second delay, before less critical alarms were triggered.
Period of Study: Data collection Jan 1st 2009- Dec 31st 2009. Data Analyses 2012
Funding: FA8650-11-2-6D03 (TIME-PO), FA8650-11-02-6D01 (ONPOINT) and W81-XWH-07-2-0118

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Stein D, Brenner M, Hu P, Zhu XS, Stansbury L, Aarabi B, Scalea T

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Results: 207 patients were enrolled. Mean age was 39 years (range 16-84), mean admission GCS 6.8 ±3.6, mean head AIS 4.3 ±0.7, and mean Marshall score 2.6 ±0.8. The in-hospital mortality was 21.7%, with 29 (14%) dying from sTBI. Of the 162 survivors, 123 had functional evaluations. 95 had good functional outcome (77%). Mean highest PTD (Pressure Time Dose) >20 and >30 occurred at 0-12 (26.9 mmHg*h, 9.6), 84-96 (28.4, 10.3), and 144-156 (33.1, 16.2) hours. When stratified by functional outcome, survivors demonstrated dramatically different temporal patterns of ICP elevation, with the first 84 hours being nearly indistinguishable between the 2 groups.

Conclusion: Although early ICH occurs, ICPs are highest later in the hospital course than traditionally described. Patterns of ICP elevation are the same in the first 3-4 days but then differ significantly based on outcome. Understanding the temporal nature of secondary insults has significant implications into developing more evidenced-based management approaches

Summary of Staff, Roles and Percent Effort by Project/Sub-project

STAFF MEMBER	ROLE	% EFFORT (%FTE)
Thomas Scalea	PI	0
Lisa Gettings	Administrator	0
Karen Murdock	Project Manager	0
Colin Mackenzie	Sub-Project PI; Vital Signs study	donated
Peter Hu	Co-Investigator	0
Yan Xiao (resigned)	Technical Support	0
Steven Seebode (resigned 10/6/10)	Technical Support	0
George Hagegeorge (hired 2/28/11)	Technical Support	0
Jessica Baroody	Technical Support	0
Shiming Yang	Student Assistant	0
Eric Lund	IT Application Engineer	0
Deborah Stein	Sub-project PI; Cytokine study	0
Kevin Sheth	Sub-project Co-PI	1
Bizhan Aarabi	Co-Investigator	0
Richard Dutton	Co-Investigator	0
Allison Lindell (resigned 7/30/11/0	Coordinator; Cytokines study	0
Kaspar Keledjian	Cytokine technician	0
Robert Rosenthal	Sub-project PI; Animal model	0
Gary Fiskum	Co-Investigator	0
Karen Volpini	Database Management	0
Madeline Mitrou (resigned 1/1/11)	Research Nurse	0
Yawei Wang	Research Nurse	0
Amechi Anozado	Research Assistant	0
Margaret Mensa	Research Nurse	0
Diane Rouse (resigned)	Research Nurse	0
Marianne Hattan	Research Nurse	0
Bonnie McManus (resigned 6/23/11)	Research Nurse	0
Keri Volpini	Research Assistant	0
Christine Wade-Mariani	Research Assistant	0
Charles Simpson (resigned)	Research Assistant	0
Scott Berry (resigned)	Research Assistant	0
Tondeleyo Gonzalez	Research Assistant	0
Carrie Sauer (resigned)	Research Assistant	0
Olga Kolesnik	Research Assistant	0
Sean Jordan (resigned)	Research Assistant	0
Sara Wade	Research Assistant	0
David Prakash (resigned 12/31/10)	Research Assistant	0

Ryan Gens (resigned)	Research Assistant	0
Cris Imle	Physical Therapist	0
Myra Collins (resigned 7/13/10)	Research Assistant	0
Jonathan Gooch	Research Assistant	0
Sean Crane	Research Assistant	0
Daniel Mayer	Research Assistant	0
Jamila Torain (hired 2/15/11)	Research Assistant	0
Emily Cooper (hired 1/18/11)	Research Assistant	0
Genna McFarland (resigned)	Student Assistant	0
Kristina Clem (resigned)	Data Entry	0
Joe Kufera	Statistician	0
Gordon Smith	Epidemiologist	0
Julie Hazleton	Technician	0
Jennifer Racz (resigned)	Technician	0
Xiaoli Xiao (resigned)	GRA	0
Wei Xiong (resigned 12/31/10)	GRA	0
Keng-Hao Liu	GRA	0
Tiffany Greco	GRA	0
Yu Wei Chang (resigned)	Data Processor	0
Ryan Seebode	Data Entry Assistant	0
Susanna Scafidi	Co-Investigator	0
Matthew Woodford (resigned 12/15/10)	Post-doctoral Fellow	0
Irina Balan	Post-doctoral Fellow	0
Rao Gulliapalli	Co-Investigator	0
Matt Lissauer	Co-Investigator	0
Jiachen Zhuo	Post-doctoral Fellow	0
Josh Ayres	Student Assistant	0
Lynn Stansbury	Medical Editor	0

* 100% effort for a GRA is 20 hours/week